REMARKS

Interview and Petition for Suspension of Action

Applicants thank Examiner Jean-Louis and her Supervisor, Sreeni Padmanabhan, for the courtesy of a personal interview on June 30, 2008 which is summarized herein. As follow-up to the interview, Applicants are in the process of generating data similar to the data presented with the January 16, 2008 response with additional surfactants to further address the obviousness rejections. However, the results of these experiments are not yet available. Applicants present herewith a petition for suspension of action under 37 C.F.R. § 1.103(a) to provide time to obtain this data. The present response is presented to timely reply to the Office Action of April 9, 2008.

The gel-cream formulation of the invention

A gel-cream formulation includes both 20-50 wt% of alcohol and 7-30 wt% of oil as components. A gel-cream formulation has good solubility of indomethacin and exhibits an excellent absorbability of the indomethacin through the skin due to the high (20-50 wt%) alcohol composition. Furthermore, the gel-cream formulation of the invention does not stick to the skin after it is used due to the oil component (7-30 wt% oil).

That is, the gel-cream formulation of the invention has the advantage of both a conventional gel formulation and a conventional cream formulation. Due to the high oil content, the gel-cream formulation of the claimed invention avoids the disadvantage of the conventional gel formulation which gives a "poor use" feeling and also avoids the disadvantage of the conventional cream formulation which has poor absorbability of indomethacin through the skin.

While gel-cream formulations are known, what has not been known and which is the problem solved by the invention is prevention of separation of the gel-cream formulation into oil and water layers due to the large amount of alcohol present in the gel-cream formulation. This problem is solved by the presently claimed invention and the resulting commercial products are marketed in Japan.

Applicants present the following comparison between the claimed invention and the cited prior art documents. The Examiner is referred to Exhibit A, attached hereto, which is identical to the color version which was discussed and presented at the interview.

Rejection under 35 U.S.C. § 103(a)

Claims 1 and 3 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kimura, et al. (JP 10-182458) (Kimura).

The formulation described in Example 2 of Kimura, et al. is a cream formulation. This formulation comprises total amount of 25 wt% of medium chain fatty acid triglyceride and diisopropyl adipate as oil component but no alcohol so phase separation is not a problem.

The formulation disclosed in Example 3 of Kimura, et al. is a gel formulation. This formulation comprises 30 wt% of modified ethanol as an alcohol, but comprises only 3 wt% of an oil component (diisopropyl adipate). Because the oil component is low and outside the range of Applicants' claimed invention (see Table in upper left side of Exhibit A), phase separation is not a problem.

Indeed, Kimura avoids combining high oil and high alcohol in the same formulation, presumably to completely avoid the phase separation problem that is addressed by Applicants' claimed invention.

Although the Examiner agrees that Kimura, et al. do not teach all of the elements of the claimed invention, present claims 1 and 3 are rejected as obvious, particularly in light of paragraph 0008 of Kimura, et al. which teaches "a surface active agent (a sorbitan fatty acid ester and a glycerine fatty acid ester, Polyglyceryl fatty acid ester, propylene glycol fatty acid ester, Polyoxyethylene sorbitan fatty acid ester, polyoxyethylene sorbitol fatty acid ester, Polyoxyethylene glycerine fatty acid ester, polyethylene glycol fatty acid ester,...)".

However, Kimura, et al. only teach surfactants which are generic to the specific surfactants claimed by Applicants. Kimura, et al. do not teach that the surfactant must have a melting point of 40 °C or higher. While the Examiner argues that such characteristic would be inherent (Office Action, page 3, paragraph 1), such property would not be inherent to the disclosure of Kimura, et al. because not all of the surfactants taught by Kimura, et al. have a melting temperature of 40 °C or higher. Only specific species within the various genera described by Kimura would fall within the scope of the claims. Furthermore, there is no guidance in Kimura, et al. for one of ordinary skill in the art to address the technical problem of phase separation defined and solved by Applicants. The disclosure of paragraph 0008 of Kimura,

et al. is merely a generic disclosure that does not specify either the size of the polymer or the nature of the fatty acid.

The Examiner argues that Kimura teaches the exact same surfactant as in the presently claimed invention (polyethylene glycol monostearate). Presumably, the Examiner refers here to Example 3. Example 2 also teaches surfactants which are within the scope of Applicants' claims. However, as discussed above, Example 2 describes an external cream agent and does not have an alcohol component. One of ordinary skill in the art would not add an alcohol component to the formulation of Example 2 because one of ordinary skill in the art would have expected the combination of oil and alcohol to result in phase separation. Accordingly, even though Example 2 teaches both the surfactant and oil components along the lines claimed by Applicants, Example 2 does not teach all of the claim elements and it would not be reasonable for one of ordinary skill in the art to modify Example 2 to add other components (thereby coming to the same invention as claimed by Applicants) because one of ordinary skill in the art would want to avoid phase separation.

Likewise in Example 3, while alcohol in the range of Applicants' claimed invention and polyethylene glycol monostearate are taught, one of ordinary skill in the art would not have further combined an oil component as one of ordinary skill in the art would have wanted to avoid phase separation.

The Examiner rebuts Applicants' arguments that the gel of Kimura is unpleasant and sticky because the gel formulation (Example 3, discussed above) has the same surfactant (polyethylene glycol monostearate) and would therefore inherently have the same characteristics. However, in reality, the gel of Example 3 would <u>not</u> be expected to have the same characteristics of the claimed gel-cream formulation because the property of "good feel" is not due to the surfactant but to the presence of the oil component which is lacking in the formulation of Example 3 of Kimura. As discussed above, the role of the surfactant in Applicants' preparations is to prevent phase separation of the oil and aqueous (alcohol) phase. As the formulations of Kimura are different from Applicants' claimed formulation, they also lack the advantageous properties of Applicants' claimed invention of "good feel" in combination with high absorption of indomethacin.

The Examiner also appears to identify the "good feel" and high indomethacin absorption properties of the claimed composition as an intended use. However, these properties of the claimed composition are a direct result of the inventive combination of 25-50 wt% alcohol, 7-30 wt% of oil component combined with a surfactant "selected from the group consisting of glyceryl monostearate, sorbitan monostearate, stearyl alcohol, and polyethylene glycol monostearate, wherein the component selected from the group consisting of glyceryl monostearate, sorbitan monostearate, stearyl alcohol, and polyethylene glycol monostearate has a melting point of 40°C or higher" and flow directly from this combination. Accordingly, properties of "good feel" and superior absorption of indomethacin should be taken into account in determining patentability.

The Examiner also mentions that Kimura teaches 20% of adipic acid oil in example 2 (Office Action, page 7, paragraph 1). However, Kimura teaches "diisopropyl adipate" not "adipic acid oil". Furthermore, the concentration is 5%, not 20%. As discussed at the interview of June 30th, the concentrations of Kimura's components are given after the naming of the ingredient, not before. Applicants respectfully submit that these comments are in error.

In view of Applicants' arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 1 and 3 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Inagi, et al. (US 4309414) (Inagi).

Example 4 of Inagi, et al. is a gel formulation, similar to Example 3 of Kimura, et al. (discussed above). The gel formulation of Inagi, et al. comprises 30 wt% of ethanol as an alcohol, but comprises only 2 wt% of oil component (diisopropyl adipate) so that the phase separation problem does not occur here.[1]

Inagi does not teach either a cream or a gel-cream formulation.

[1] Note that the polyethylene glycol 300 of Inagi, et al. is different chemically from polyethylene glycol monostearate as recited in claim 1 of the present invention. The chemical formulas are different as illustrated by the technical bulletins provided at the interview (Handbook of Pharmaceutical Excipients, 3rd edition, Arthur H. Kibbe, ed.) and provided herewith as Exhibits B and C.

The Office Action refers to col. 2, lines 14-16 as teaching addition of an oil component (Office Action, page 6, lines 2-3; 2nd full paragraph). However, the components listed here are more properly classified as surfactants, rather than oils.

The Office Action also states that polyethylene glycol 300 is the same as polyethylene glycol 300 monostearate which is incorrect. At the interview of June 30th, technical bulletins for these compounds were submitted so that they could be clearly distinguished (see interview summary herein; Examiner's interview summary under "Exhibit shown or demonstration conducted" (indicated as "samples of the prior art references"); and Exhibit B and C attached hereto).

Accordingly, Inagi does not teach all of the elements of the claimed invention. In view of Applicants' arguments, withdrawal of the rejection is respectfully requested.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

In view of the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Sept 8, 2008

By: _____

Che Swyden Chereskin, Ph.D.
Registration No. 41,466
Agent of Record
Customer No. 20,995
(949) 721-6385

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EXHIBIT A

Table. 1

The present invention

Claim (gel-cream agent)	(wt%)	
Indomethacin	0.1～3	A
Alcohol (C1-C3)	25～50	B
Gelling agent	0.01～5	C
Oil Component	7～30	D
Water	20～50	E
Sorbitan monostearate Glyceryl monostearate Polyethylene glycol monostearate Stearyl alcohol	0.01～10	F

A: Active ingredient
B: Alcohol
C: Gelling agent
D: Oil component
E: Water
F: Surfactant

Cited Document

Kimura JP 10-182458 Example 2 (External cream agent)	(wt%)	A+D+E+F
Indomethacin	1.0	A
Chlorpheniramine maleate	0.5	
Medium chain fatty acid triglyceride	20.0	D
Diisopropyl adipate	5.0	D
Propylene glycol	12.0	
Polyoxyethylene sorbitan monostearate	6.0	
Sorbitan monostearate	3.0	F
Glyceryl monostearate	8.0	F
Purified water	Total 100	E

Kimura JP 10-182458 Example 3 (gel agent)	(wt%)	A+B+C+E+F
Indomethacin	0.5	A
Chlorpheniramine maleate	0.01	
Polyethylene glycol monostearate	5.0	F
Diisopropyl adipate	3.0	(D)
1,3-Butylene glycol	8.0	
Polyvinyl pyrrolidone	0.5	
Carboxyvinyl polymer	1.5	C
Diisopropanolamine	proper quantity	
Modified ethanol	30.0	B
Purified water	Total 100	E

Inagi US 4,309,414 Example 4(gel agent)	(g)	A+B+C+E
Carboxyvinyl polymer	1.0	C
Hydroxyethylcellulose	1.0	
Indomethacin	1.0	A
Polyethylene glycol 300	10.0	
Ethanol	30.0	B
Diisopropyl adipate	2.0	(D)
Diisopropanolamine	0.9	
Purified water	Total 100	E

EXHIBIT B

Polyethylene Glycol

1. Nonproprietary Names

BP: Macrogol 300
Macrogol 400
Macrogol 1000
Macrogol 1540
Macrogol 4000
Macrogol 6000
Macrogol 20 000
Macrogol 35 000

JP: Macrogel 400
Macrogel 1500
Macrogel 4000
Macrogel 6000
Macrogel 20 000

PhEur: Macrogolum 300
Macrogolum 400
Macrogolum 1000
Marcogolum 1500
Macrogolum 3000
Macrogol 4000
Macrogol 6000
Macrogol 20 000
Macrogol 35 000

US: Polyethylene glycol

2. Synonyms

Breox PEG; *Carbowax*; *Hodag PEG*; *Lutrol E*; PEG; polyoxyethylene glycol.

3. Chemical Name and CAS Registry Number

α-Hydro-ω-hydroxy-poly(oxy-1,2-ethanediyl) [25322-68-3]

4. Empirical Formula Molecular Weight

$HOCH_2(CH_2OCH_2)_mCH_2OH$

Where m represents the average number of oxyethylene groups.

Alternatively, the general formula $H(OCH_2CH_2)_nOH$ may be used to represent polyethylene glycol, where n is a number one more than the value of m in the previous formula.

See Table I for the average molecular weights of typical polyethylene glycols. Note that the number which follows PEG indicates the average molecular weight of the polymer.

5. Structural Formula

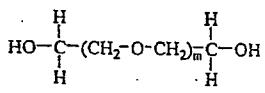

Table I: Structural formula and molecular weight of typical polyethylene glycol polymers.

Grade	m	Average molecular weight
PEG 200	4.2	190-210
PEG 300	6.4	285-315
PEG 400	8.7	380-420
PEG 540 (blend)	—	500-600
PEG 600	13.2	570-613
PEG 900	15.3	855-900
PEG 1000	22.3	950-1050
PEG 1450	32.5	1300-1600
PEG 1540	28-36	1300-1600
PEG 2000	40-50	1800-2200
PEG 3000	60-75	2700-3300
PEG 3350	75.7	3000-3700
PEG 4000	69-84	3000-4800
PEG 4600	104.1	4400-4800
PEG 8000	181.4	7000-9000

6. Functional Category

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

7. Applications in Pharmaceutical Formulation or Technology

Polyethylene glycols are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations.

Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin, *see* Section 14. Although they do not readily penetrate the skin, polyethylene glycols are water soluble and as such are easily removed from the skin by washing; they are therefore useful as ointment bases.[1] Solid grades are generally employed in topical ointments with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol.

Mixtures of polyethylene glycols can be used as suppository bases[2] where they have the following advantages over fats: the melting point of the suppository can be made higher to withstand exposure to warmer climates; release of the drug is not dependent upon melting point; physical stability on storage is better; suppositories are readily miscible with rectal fluids. Disadvantages of using polyethylene glycols are: they are chemically more reactive than fats; greater care is needed in processing to avoid inelegant contraction holes in the suppositories; the rate of release of water-soluble medications decreases with the increasing molecular weight of the polyethylene glycol; polyethylene glycols tend to be more irritating to mucous membranes than fats.

Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers.

Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. However, they may cause hardening of the capsule shell by preferential absorption of moisture from gelatin in the shell.

In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.

In solid-dosage formulations, higher molecular weight polyethylene glycols can enhance the effectiveness of tablet binders and impart

plasticity to granules.[3] However, they have only limited binding action when used alone, and can prolong disintegration if present in concentrations greater than 5% w/w. When used for thermoplastic granulations,[4-6] a mixture of the powdered constituents with 10-15% w/w PEG 6000 is heated to 70-75°C. The mass becomes paste-like and forms granules if stirred while cooling. This technique is useful for the preparation of dosage forms such as lozenges when prolonged disintegration is required.

Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol.[7] Animal studies have also been performed using polyethylene glycols as solvents for steroids in osmotic pumps.

In film coatings, solid grades of polyethylene glycol can be used alone for the film coating of tablets or can be useful as hydrophilic polishing materials. Solid grades are also widely used as plasticizers in conjunction with film-forming polymers.[7] The presence of polyethylene glycols, especially liquid grades, in film coats tends to increase their water permeability and may reduce protection against low pH in enteric-coating films. Polyethylene glycols are useful as plasticizers in microencapsulated products to avoid rupture of the coating film when the microcapsules are compressed into tablets.

Polyethylene glycol grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets. The lubricant action is not as good as that of magnesium stearate, and stickiness may develop if the material becomes too warm during compression. An antiadherent effect is also exerted, again subject to the avoidance of over-heating.

In addition, polyethylene glycols have been used in the preparation of urethane hydrogels which are used as controlled-release agents.

8. Description

The USP describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200-600 are liquids; grades 1000 and above are solids at ambient temperatures.

Liquid grades (PEG 200-600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight, but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures.

Solid grades (PEG >1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free-flowing milled powders.

9. Pharmacopeial Specifications

See Table II.

10. Typical Properties

Density:
1.11-1.14 g/cm^3 at 25°C for liquid PEGs;
1.15-1.21 g/cm^3 at 25°C for solid PEGs.

Flash point:
182°C for PEG 200;
213°C for PEG 300;
238°C for PEG 400;
250°C for PEG 600.

Freezing point:
< -65°C PEG 200 sets to a glass;
-15 to -8°C for PEG 300;
4-8°C for PEG 400;
15-25°C for PEG 600.

Melting point:
37-40°C for PEG 1000;
44-48°C for PEG 1500;
40-48°C for PEG 1540;
45-50°C for PEG 2000;
48-54°C for PEG 3000;
50-58°C for PEG 4000;
55-63°C for PEG 6000;
60-63°C for PEG 8000;
60-63°C for PEG 20 000.

Moisture content: liquid polyethylene glycols are very hygroscopic, although hygroscopicity decreases with increasing molecular weight. Solid grades, e.g., PEG 4000 and above, are not hygroscopic. *See* Figs. 1-3.[a]

Particle size distribution: *see* Figs. 4-7.[a]

Refractive index:
n_D^{25} = 1.459 for PEG 200;
n_D^{25} = 1.463 for PEG 300;
n_D^{25} = 1.465 for PEG 400;
n_D^{25} = 1.467 for PEG 600.

Solubility: all grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher molecular weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol, and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

Surface tension: approximately 44 mN/m (44 dynes/cm) for liquid polyethylene glycols; approximately 55 mN/m (55 dynes/cm) for 10% w/v aqueous solution of solid polyethylene glycol.

Viscosity (*kinematic*): *see* Tables III and IV.

[a] *Handbook of Pharmaceutical Excipients*, First Edition.

11. Stability and Storage Conditions

Polyethylene glycols are chemically stable in air and in solution although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, nor do they become rancid.

Polyethylene glycols and aqueous polyethylene glycol solutions can be sterilized by autoclaving, filtration, or gamma irradiation.[9] Sterilization of solid grades by dry heat at 150°C for 1 hour may induce oxidation, darkening, and the formation of acidic degradation products. Ideally, sterilization should be carried out in an inert atmosphere. Oxidation of polyethylene glycols may also be inhibited by the inclusion of a suitable antioxidant.

If heated tanks are used to maintain solid polyethylene glycols in a molten state, care must be taken to avoid contamination with iron, which can lead to discoloration. The temperature must be kept to the minimum necessary to ensure fluidity; oxidation may occur if polyethylene glycols are exposed for long periods to temperatures exceeding 50°C. However, storage under nitrogen reduces the possibility of oxidation.

Polyethylene glycols should be stored in well-closed containers in a cool, dry, place. Stainless steel, aluminum, glass, or lined steel containers are preferred for the storage of liquid grades.

Table II: Pharmacopeial specifications of polyethylene glycol.

Test	JP PEG 400	JP 1500	JP 4000	JP 6000	JP 20 000	PhEur 300	PhEur 400	PhEur 1000	PhEur 1500	PhEur 4000	USP
Appearance of solution	—	+	+	+	+	+	+	+	+	+	+
Characters	+	+	+	+	+	+	+	+	+	+	—
Freezing point	—	—	—	—	—	—	—	35-40°C	42-48°C	53-58°C	—
Congealing point	—	37-41°C	53-57°C	56-61°C	56-64°C						
Viscosity	—	—	—	—	—	+	+	+	+	+	*See* Table III
Average molecular weight	380-420	—	2600-3800	7300-9300	15 000-25 000	+	+	+	+	+	*See* Table III
Acidity/alkalinity	+	+	+	+	+	+	+	+	+	+	—
pH (5% w/v solution)	4.0-7.0	4.0-7.0	4.0-7.5	4.5-7.5	4.5-7.5	—	—	—	4.0-7.0	4.5-7.5	4.5-7.5
Hydroxyl value	340-394	264-300	—	—	—	340-394	264-300	107-118	70-80	25-32	—
Reducing substances	—	—	—	—	—	+	+	+	+	+	—
Residue on ignition	≤ 0.1%	≤ 0.1%	≤ 0.25%	≤ 0.25%	≤ 0.25%	—	—	—	—	—	≤ 0.1%
Sulfated ash	—	—	—	—	—	≤ 0.2%	≤ 0.2%	≤ 0.2%	≤ 0.2%	≤ 0.2%	—
Limit of ethylene glycol and diethylene glycol	≤ 0.25%	+	—	—	—	≤ 0.4%	≤ 0.4%	—	—	—	≤ 0.25%
Ethylene oxide	—	—	—	—	—	≤ 1 ppm	≤ 1 ppm	≤ 1 ppm	≤ 1 ppm	≤ 1 ppm	≤ 10 ppm
1,4-dioxane	—	—	—	—	—	—	—	—	—	—	≤ 10 ppm
Heavy metals	≤ 20 ppm	≤ 20 ppm	—	—	—	≤ 20 ppm	≤ 20 ppm	≤ 20 ppm	≤ 20 ppm	≤ 20 ppm	≤ 5 ppm
Organic volatile impurities	—	—	—	—	—	—	—	—	—	—	+
Water	≤ 1.0%	≤ 1.0%	≤ 1.0%	≤ 1.0%	≤ 1.0%	≤ 2.0%	≤ 2.0%	≤ 2.0%	≤ 1.0%	≤ 1.0%	—

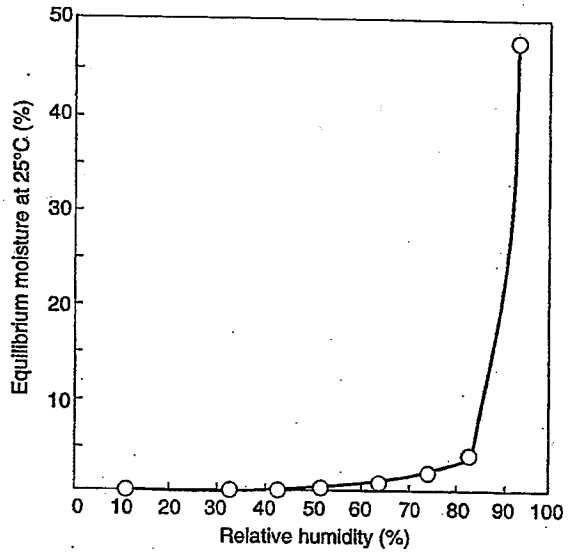

Fig. 1: Equilibrium moisture content of PEG 4000 (McKesson, Lot #B192-8209) at 25°C.

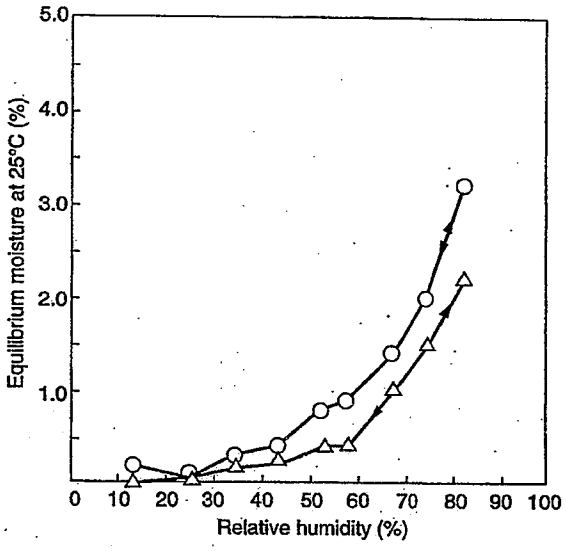

Fig. 2: Equilibrium moisture content of PEG 4000 at 25°C.
○ : PEG 4000 powder (Union Carbide Corp, Lot #B-251)
△ : PEG E-4000 (BASF, Lot #WPYA-575B)

12. Incompatibilities

The chemical reactivity of polyethylene glycols is mainly confined to the two terminal hydroxyl groups, which can be either esterified or etherified. However, all grades can exhibit some oxidizing activity due to the presence of peroxide impurities and secondary products formed by autoxidation.

Liquid and solid polyethylene glycol grades may be incompatible with some colors.

The antibacterial activity of certain antibiotics, particularly penicillin and bacitracin, is reduced in polyethylene glycol bases. The preservative efficacy of the parabens may also be impaired due to binding with polyethylene glycols.

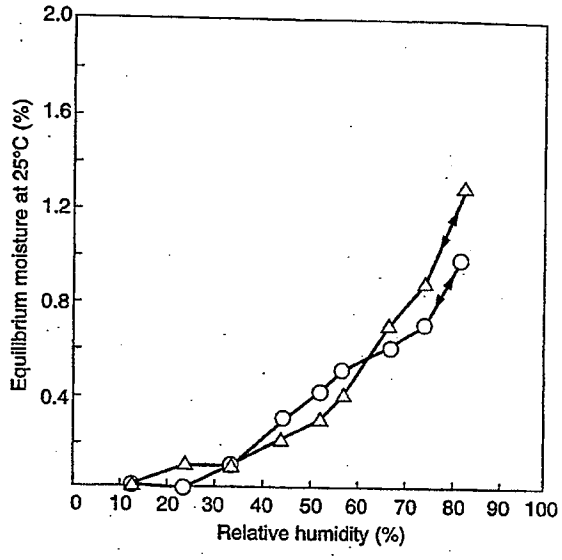

Fig. 3: Equilibrium moisture content of PEG 6000 at 25°C.
○ : PEG 6000 powder (Union Carbide Corp, Lot #B-507)
△ : PEG E-6000 (BASF, Lot #WPNA-124B)

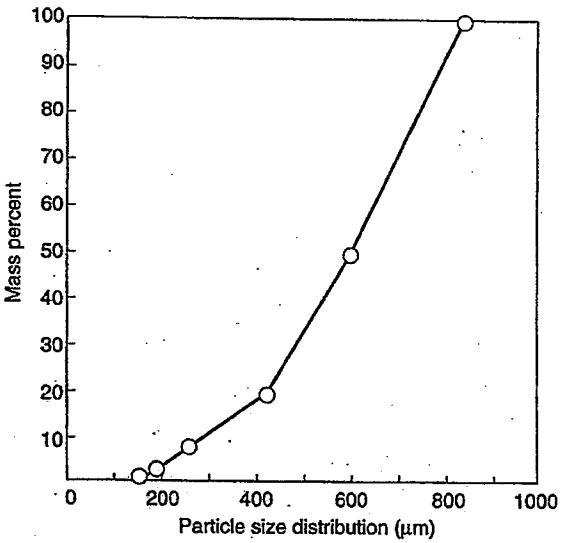

Fig. 4: Particle size distribution of PEG 4000 flakes.

Physical effects caused by polyethylene glycol bases include softening and liquefaction in mixtures with phenol, tannic acid, and salicylic acid. Discoloration of sulfonamides and dithranol can also occur and sorbitol may be precipitated from mixtures. Plastics, such as polyethylene, phenolformaldehyde, polyvinyl chloride, and cellulose-ester membranes (in filters) may be softened or dissolved by polyethylene glycols. Migration of polyethylene glycol can occur from tablet-film coatings, leading to interaction with core components.

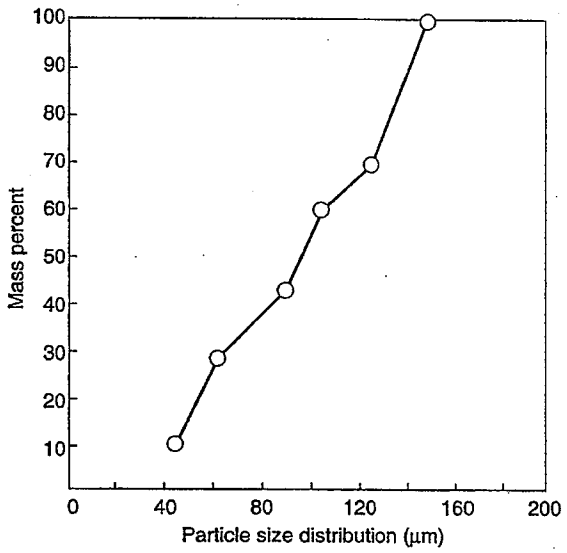

Fig. 5: Particle size distribution of PEG 4000 powder.

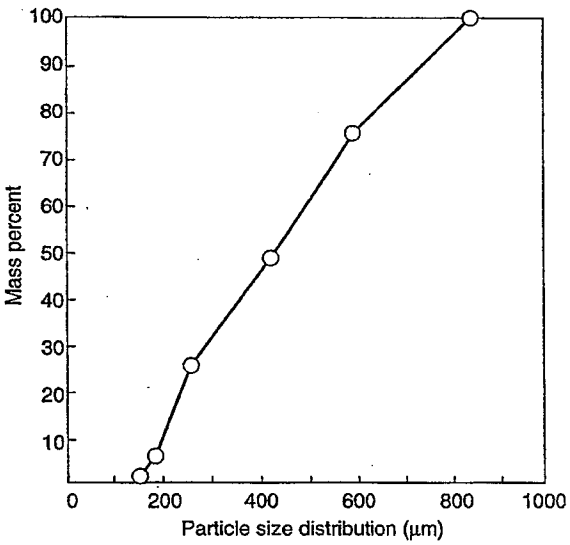

Fig. 6: Particle size distribution of PEG 6000 flakes.

13. Method of Manufacture

Polyethylene glycols are condensation polymers formed by the reaction of ethylene oxide and water under pressure in the presence of a catalyst.

14. Safety

Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials.[10-12] However, adverse reactions to polyethylene glycols have been reported and although of relatively low toxicity, any toxicity appears to be greatest with polyethylene glycols of low molecular weight.

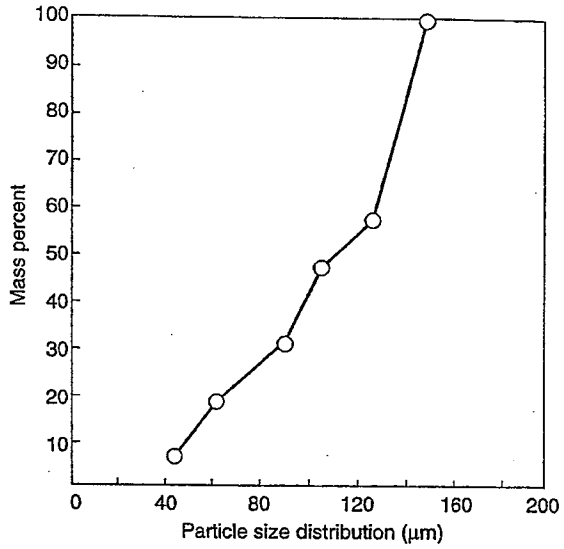

Fig. 7: Particle size distribution of PEG 6000 powder.

Polyethylene glycols administered topically may cause stinging, especially when applied to mucous membranes. Hypersensitivity reactions to polyethylene glycols applied topically, including urticaria and delayed allergic reactions, have also been reported.[13] However, the most serious adverse effects associated with polyethylene glycols are hyperosmolarity, metabolic acidosis, and renal failure following the topical use of polyethylene glycols in burn patients.[14] Topical preparations containing polyethylene glycols should therefore be used cautiously in patients with renal failure, extensive burns, or open wounds.

Oral administration of large quantities of polyethylene glycols can have a laxative effect. Therapeutically, up to 4 L of an aqueous mixture of electrolytes and high molecular weight polyethylene glycol is consumed by patients undergoing bowel cleansing.[15]

Liquid polyethylene glycols may be absorbed when taken orally, but the higher molecular weight polyethylene glycols are not significantly absorbed from the gastrointestinal tract. Absorbed polyethylene glycol is excreted largely unchanged in the urine although polyethylene glycols of low molecular weight may be partially metabolized.

The WHO has set an estimated acceptable daily intake of polyethylene glycols at up to 10 mg/kg body-weight.[16]

In parenteral products, the maximum recommended concentration of PEG 300 is approximately 30% v/v since hemolytic effects have been observed at concentrations greater than about 40% v/v.

For animal toxicity data *see* Table V.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended.

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (dental preparations, IM and IV injections, ophthalmic preparations, oral

Table III: Specification for viscosity of polyethylene glycol of nominal molecular weight at 98.9°C ± 0.3°C from the USP.

Nominal average molecular weight	Viscosity range in mm^2/s (cSt)
200	3.9-4.8
300	5.4-6.4
400	6.8-8.0
500	8.3-9.6
600	9.9-11.3
700	11.5-13.0
800	12.5-14.5
900	15.0-17.0
1000	16.0-19.0
1100	18.0-22.0
1200	20.0-24.5
1300	22.0-27.5
1400	24-30
1450	25-32
1500	26-33
1600	28-36
1700	31-39
1800	33-42
1900	35-45
2000	38-49
2100	40-53
2200	43-56
2300	46-60
2400	49-65
2500	51-70
2600	54-74
2700	57-78
2800	60-83
2900	64-88
3000	67-93
3250	73-105
3350	76-110
3500	87-123
3750	99-140
4000	110-158
4250	123-177
4500	140-200
4750	155-228
5000	170-250
5500	206-315
6000	250-390
6500	295-480
7000	350-590
7500	405-735
8000	470-900

Table IV: Viscosity of selected polyethylene glycols at 25°C and 99°C.

Grade	Viscosity in mm^2/s (cSt)	
	25°C	99°C
PEG 200	39.9	4.4
PEG 300	68.8	5.9
PEG 400	90.0	7.4
PEG 600	131	11.0
PEG 1000 solid	19.5	—
PEG 2000 solid	47	—
PEG 4000 solid	180	—
PEG 6000 solid	580	—
PEG 20 000 solid	6900	—

Table V: Animal toxicity data (LD_{50}) for various grades of polyethylene glycol.[17]

PEG grade	LD_{50} in g/kg									
	Guinea pig (oral)	Mouse (IP)	Mouse (IV)	Mouse (oral)	Rabbit (oral)	Rabbit (SC)	Rat (IP)	Rat (IV)	Rat (oral)	Rat (SC)
PEG 200	—	7.5	—	38.3	19.9	—	—	—	28.9	—
PEG 300	19.6	—	—	—	17.3	—	17	—	27.5	—
PEG 400	15.7	10.0	8.6	28.9	26.8	—	9.7	7.3	30.2	—
PEG 810	—	—	—	—	—	—	—	13	—	16
PEG 1000	22.5	20	—	—	—	—	—	—	42	—
PEG 1540	—	—	—	—	—	—	15.4	—	51.2	—
PEG 4000	50.9	—	16	—	76	18	11.6	—	50	—
PEG 6000	50	—	—	—	—	—	6.8	—	50	—

capsules, solutions, syrups and tablets, rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Polyethylene glycols are described in many pharmacopeias.

Some pharmacopeias, such as the US, have a single monograph describing various different grades; other pharmacopeias have individual monographs. The BP for example has separate monographs for PEG 300, PEG 400, PEG 1000, PEG 1500, PEG 3000, PEG 4000, PEG 6000, PEG 20 000, and PEG 35 000.

18. Related Substances

Polyoxyethylene alkyl ethers; polyoxyethylene sorbitan fatty acid esters; suppository bases.

19. Comments

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22. Authors

JC Price.

EXHIBIT C

Polyoxyethylene Stearates

1. Nonproprietary Names

The polyoxyethylene stearates are a series of polyethoxylated derivatives of stearic acid. Of the large number of different materials commercially available, two types are listed in the USP.

JP: Polyoxyl 40 stearate
USP: Polyoxyl 40 stearate
USP: Polyoxyl 50 stearate

See also Sections 2, 3, 4, 5, and 17.

2. Synonyms

Polyoxyethylene stearates are nonionic surfactants produced by polyethoxylation of stearic acid. Two systems of nomenclature are used for these materials. The number '8' in the names 'poloxyl 8 stearate' or 'polyoxyethylene 8 stearate' refers to the approximate polymer length in oxyethylene units. The same material may also be designated 'polyoxyethylene glycol 400 stearate' or 'macrogol stearate 400' in which case, the number '400' refers to the average molecular weight of the polymer chain.

Synonyms applicable to polyoxyethylene stearates are shown below:

Ethoxylated fatty acid esters; macrogol stearates; *Marlosol*; PEG fatty acid esters; PEG stearates; polyethylene glycol stearates; poly(oxy-1,2-ethanediyl) α-hydro-ω-hydroxy-octadecanoate; polyoxyethylene glycol stearates.

Table I shows synonyms for specific materials.

3. Chemical Name and CAS Registry Number

Polyethylene glycol stearate [9004-99-3]
Polyethylene glycol distearate [9005-08-7]

Table I: Synonyms of selected polyoxyethylene stearates and distearates.

Name	Synonym
Polyoxyl 2 stearate	*Hodag DGS*; PEG-2 stearate.
Polyoxyl 4 stearate	*Acconon 200-MS*; *Hodag 20-S*; PEG-4 stearate; polyoxyethylene (4) monostearate; polyethylene glycol 200 monostearate; *Protamate 200-DPS*.
Polyoxyl 6 stearate	*Cerasynt 616*; *Kessco PEG 300 Monostearate*; *Lipal 300S*; *Lipo PEG 3-S*; PEG-6 stearate; polyethylene glycol 300 monostearate; *Polystate C*; polyoxyethylene (6) monostearate; *Protamate 300-DPS*.
Polyoxyl 8 stearate	*Acconon 400-MS*; *Cerasynt 660*; *Cithrol 4MS*; *Crodet S8*; *Emerest 2640*; *Grocor 400*; *Hodag 40-S*; *Kessco PEG-400 Monostearate*; macrogol stearate 400; *Myrj 45*; PEG-8 stearate; *Pegosperse 400 MS*; polyethylene glycol 400 monostearate; polyoxyethylene (8) monostearate; *Protamate 400-DPS*; *Ritapeg 400 MS*.
Polyoxyl 12 stearate	*Hodag 60-S*; *Kessco PEG 600 Monostearate*; *Lipo-PEG 6-S*; PEG-12 stearate; *Pegosperse 600 MS*; polyethylene glycol 600 monostearate; polyoxyethylene (12) monostearate; *Protamate 600-DPS*.
Polyoxyl 20 stearate	*Cerasynt 840*; *Hodag 100-S*; *Kessco PEG 1000 Monostearate*; *Lipo-PEG 10-S*; *Myrj 49*; *Pegosperse 1000 MS*; PEG-20 stearate; polyethylene glycol 1000 monostearate; polyoxyethylene (20) monostearate; *Protamate 1000-DPS*.
Polyoxyl 30 stearate	*Myrj 51*; PEG-30 stearate; polyoxyethylene (30) stearate.
Polyoxyl 40 stearate	*Crodet S40*; E431; *Emerest 2672*; *Hodag POE (40) MS*; *Lipal 395*; macrogol stearate 2000; *Myrj 52*; PEG-40 stearate; polyoxyethylene glycol 2000 monostearate; polyoxyethylene (40) monostearate; *Protamate 2000-DPS*.
Polyoxyl 50 stearate	*Atlas G-2153*; *Crodet S50*; *Lipal 505*; *Myrj 53*; PEG-50 stearate; polyoxyethylene (50) monostearate.
Polyoxyl 100 stearate	*Myrj 59*; PEG-100 stearate; polyethylene glycol 4400 monostearate; polyoxyethylene (100) monostearate; *Protamate 4400-DPS*.
Polyoxyl 150 stearate	*Hodag 600-S*; PEG-150 stearate.
Polyoxyl 4 distearate	*Hodag 22-S*; PEG-4 distearate.
Polyoxyl 8 distearate	*Hodag 42-S*; *Kessco PEG 400 DS*; PEG-8 distearate; polyethylene glycol 400 distearate; *Protamate 400-DS*.
Polyoxyl 12 distearate	*Hodag 62-S*; *Kessco PEG 600 Distearate*; PEG-12 distearate; polyethylene (12) distearate; polyethylene glycol 600 distearate; *Protamate 600-DS*.
Polyoxyl 32 distearate	*Hodag 154-S*; *Kessco PEG 1540 Distearate*; PEG-32 distearate; polyethylene glycol 1540 distearate; polyoxyethylene (32) distearate.
Polyoxyl 150 distearate	*Hodag 602-S*; *Kessco PEG 6000 DS*; PEG-150 distearate; polyethylene glycol 6000 distearate; polyoxyethylene (150) distearate; *Protamate 6000-DS*.

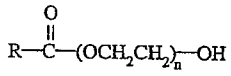
4. Empirical Formula Molecular Weight

See Table II.

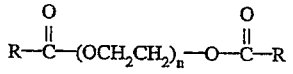
Table II: Empirical formula and molecular weight of selected polyoxyethylene stearates.

Name	Empirical Formula	Molecular Weight
Polyoxyl 6 stearate	$C_{30}H_{60}O_8$	548.80
Polyoxyl 8 stearate	$C_{34}H_{68}O_{10}$	636.91
Polyoxyl 12 stearate	$C_{42}H_{84}O_{14}$	813.12
Polyoxyl 20 stearate	$C_{58}H_{116}O_{22}$	1165.55
Polyoxyl 40 stearate	$C_{98}H_{196}O_{42}$	2046.61
Polyoxyl 50 stearate	$C_{118}H_{236}O_{52}$	2487.15
Polyoxyl 100 stearate	$C_{218}H_{436}O_{102}$	4689.80

5. Structural Formula



For the monostearate; where the average value of n is 6 for polyoxyl 6 stearate, 8 for polyoxyl 8 stearate, etc.



For the distearate; where the average value of n is 12 for polyoxyl 12 distearate, 32 for polyoxyl 32 distearate, etc.

In both structures, R represents the alkyl group of the parent fatty acid. With stearic acid, R is $CH_3(CH_2)_{16}$. However, it should be noted that stearic acid usually contains other fatty acids, primarily palmitic acid, and consequently a polyoxyethylene stearate may also contain varying amounts of other fatty acid derivatives such as palmitates.

6. Functional Category

Emulsifying agent; solubilizing agent; wetting agent.

7. Applications in Pharmaceutical Formulation or Technology

Polyoxyethylene stearates are generally used as emulsifiers in oil-in-water-type creams and lotions. Their hydrophilicity or lipophilicity depends on the number of ethylene oxide units present: the larger the number, the greater the hydrophilic properties. Polyoxyl 40 stearate has also been used as an emulsifying agent in intravenous infusions.[1]

Polyoxyethylene stearates are particularly useful as emulsifying agents when astringent salts or other strong electrolytes are present. They can also be blended with other surfactants to obtain any hydrophilic-lipophilic balance for lotions or ointment formulations.

Use	Concentration (%)
Auxiliary emulsifier for o/w intravenous fat emulsion	0.5-5
Emulsifier for o/w creams or lotions	0.5-10
Ophthalmic ointment	7
Suppository component	1-10
Tablet lubricant	1-2

8. Description

Name	Description
Polyoxyl 6 stearate	Soft solid
Polyoxyl 8 stearate	Waxy cream
Polyoxyl 12 stearate	Pasty solid
Polyoxyl 20 stearate	Waxy solid
Polyoxyl 40 stearate	Waxy solid, with a faint, bland, fat-like odor, off-white to light tan in color.
Polyoxyl 50 stearate	Solid, with a bland, fat-like odor or odorless.
Polyoxyl 100 stearate	Solid
Polyoxyl 12 distearate	Paste
Polyoxyl 32 distearate	Solid
Polyoxyl 150 distearate	Solid

9. Pharmacopeial Specifications

Test	JP Polyoxyl 40 stearate	USP Polyoxyl 40 stearate	USP Polyoxyl 50 stearate
Identification	—	+	+
Characters	+	—	—
Clarity and color of solution	+	—	—
Congealing range	39.0-44.0°C	37-47°C	—
Congealing point of the fatty acid	≥ 53 °C	—	—
Residue on ignition	≤ 0.10%	—	—
Water	—	≤ 3.0%	≤ 3.0%
Arsenic	≤ 3 ppm	—	≤ 3 ppm
Heavy metals	≤ 10 ppm	≤ 0.001%	≤ 0.001%
Acid value	≤ 1	≤ 2	≤ 2
Hydroxyl value	—	25-40	23-35
Saponification value	25-35	25-35	20-28
Free polyethylene glycols	—	17-27%	17-27%
Organic volatile impurities	—	+	+

10. Typical Properties

Flash point:
> 149°C for poloxyl 8 stearate (*Myrj 45*).

Solubility:

Name	Solvent		
	Ethanol (95%)	Mineral oil	Water
Polyoxyl 6 stearate	S	S	DH
Polyoxyl 8 stearate	S	I	D
Polyoxyl 12 stearate	S	I	S
Polyoxyl 20 Stearate	S	I	S
Polyoxyl 40 stearate	S	I	S
Polyoxyl 50 stearate	S	I	S
Polyoxyl 100 stearate	S	I	S
Polyoxyl 12 distearate	S	—	DH
Polyoxyl 32 distearate	S	—	S
Polyoxyl 150 distearate	I	—	S

Where,

D = dispersible
I = insoluble
S = soluble
DH = dispersible (with heat)

See also Table III.

11. Stability and Storage Conditions

Polyoxyethylene stearates are generally stable in the presence of electrolytes and weak acids or bases. Strong acids and bases can cause gradual hydrolysis and saponification.

The bulk material should be stored in a well-closed container, in a dry place, at room temperature.

12. Incompatibilities

Polyoxyethylene stearates are unstable in hot alkaline solutions due to hydrolysis, and will also saponify with strong acids or bases. Discoloration or precipitation can occur with salicylates, phenolic substances, iodine salts, and salts of bismuth, silver, and tannins.[2-4] Complex formation with preservatives may also occur.[5]

Table III: Typical properties of polyoxyethylene stearates.

Name	Acid value	Free ethylene oxide	HLB value	Hydroxyl value	Iodine number	Melting point (°C)	Saponification value	Water content (%)
Polyoxyl 6 stearate	≤ 5.0	≤ 100 ppm	9.7	—	≤ 0.5	28-32	95-110	—
Polyoxyl 8 stearate	≤ 2.0	≤ 100 ppm	11.1	87-105	≤ 1.0	28-33	82-95	≤ 3.0
Polyoxyl 12 stearate	≤ 8.5	≤ 100 ppm	13.6	55-75	≤ 1.0	≈ 37	62-78	≤ 1.0
Polyoxyl 20 stearate	≤ 1.0	≤ 100 ppm	14	50-62	≤ 1.0	≈ 28	46-56	≤ 1.0
Polyoxyl 30 stearate	≤ 2.0	—	16	35-50	—	—	30-45	≤ 3.0
Polyoxyl 40 stearate	≤ 1.0	—	16.9	27-40	—	≈ 38	25-35	≤ 3.0
Polyoxyl 50 stearate	≤ 2.0	—	17.9	23-35	—	≈ 42	20-28	≤ 3.0
Polyoxyl 100 stearate	≤ 1.0	≤ 100 ppm	18.8	15-30	—	≈ 46	9-20	≤ 3.0
Polyoxyl 8 distearate	≤ 10.0	—	—	≤ 15	≤ 0.5	≈ 36	115-124	—
Polyoxyl 12 distearate	≤ 10.0	≤ 100 ppm	10.6	≤ 20	≤ 1.0	≈ 39	93-102	≤ 1.0
Polyoxyl 32 distearate	≤ 10.0	≤ 100 ppm	14.8	≤ 20	≤ 0.25	≈ 45	50-62	≤ 1.0
Polyoxyl 150 distearate	7-9	≤ 100 ppm	18.4	≤ 15	≤ 0.1	53-57	14-20	≤ 1.0

The antimicrobial activity of some materials such as bacitracin, chloramphenicol, phenoxymethylpenicillin, sodium penicillin, and tetracycline may be reduced in the presence of polyoxyethylene stearate concentrations greater than 5% w/w.[6,7]

13. Method of Manufacture

Polyoxyethylene stearates are prepared by the direct reaction of fatty acids, particularly stearic acid, with ethylene oxide.

14. Safety

Although polyoxyethylene stearates are primarily used as emulsifying agents in topical pharmaceutical formulations certain materials, particularly polyoxyl 40 stearate, have also been used in intravenous injections and oral preparations.[1,4]

Polyoxyethylene stearates have been extensively tested for toxicity in animals[8-13] and are widely used in pharmaceutical formulations and cosmetics. They are generally regarded as essentially nontoxic and nonirritant materials.

Polyoxyl 8 stearate:

LD_{50} (hamster, oral): 27 g/kg[14]
LD_{50} (rat, oral): 64 g/kg

Polyoxyl 20 stearate:

LD_{50} (mouse, IP): 0.2 g/kg[14]
LD_{50} (mouse, IV): 0.87 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

Polyoxyethylene stearates that contain greater than 100 ppm of free ethylene oxide may present an explosion hazard when stored in a closed container. This is due to the release of ethylene oxide into the container headspace where it can accumulate, and so exceed the explosion limit.

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (dental solutions, IV injections, ophthalmic preparations, oral capsules and tablets, otic suspensions, topical creams, emulsions, lotions, ointments and solutions, and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Name	Pharmacopeia
Polyoxyl 40 stearate	Jpn, US.
Polyoxyl 50 stearate	US.

18. Related Substances

Polyethylene glycol; stearic acid.

19. Comments

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